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Dose-Dependent Antihypertensive Efficacy and Tolerability of Perindopril in a Large, Observational, 12-Week, General Practice-Based Study

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Abstract

Background: Current guidelines recommend the use of full therapeutic dosages of antihypertensive agents, or combination therapy, to improve BP control of hypertensive patients in primary healthcare.

Objective: The aim of this study was to assess the dose-dependent antihypertensive efficacy and safety of perindopril 4 and 8 mg/day in the clinical setting.

Study Design and Setting: The CONFIDENCE study was a prospective, observational, multicenter trial. This was a real-world, clinic-based, outpatient study involving 880 general practitioners/primary-care clinics and 113 specialists in Canada.

Patients: The study included untreated or inadequately managed patients with hypertension (i.e. seated BP ≥140/90 mmHg, or ≥130/80 mmHg in the presence of diabetes mellitus, renal disease, or proteinuria) without coronary artery disease (CAD).

Intervention: Treatment consisted of perindopril 4 mg/day, uptitrated to 8 mg/day as required for BP control at visit 2, for 12 weeks. Among the patients already being treated at baseline, perindopril either directly replaced all previous ACE inhibitors or angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]), or was added to antihypertensive treatment with calcium channel blockers (CCBs), diuretics, or β-adrenoceptor antagonists (β-blockers).

Main Outcomes Measures: The primary outcomes were the mean changes in BP from baseline following treatment with perindopril 4 and 8 mg/day as well as the proportion of patients achieving BP control (BP <140/90 mmHg, or <130/80 mmHg in diabetic patients) in the intent-to-treat (ITT) population. Secondary analyses included the incidence of adverse events and compliance.

Results: A total of 8298 hypertensive patients entered the study: 56% with newly diagnosed hypertension and 44% with uncontrolled hypertension. Mean SBP/DBP decreased significantly from baseline (152.5 ± 10.8/89.5 ± 9 mmHg) over 12 weeks (–18.5/–9.7 mmHg; $p < 0.001$). At visit 2, 23% of patients were uptitrated to perindopril 8 mg/day, which resulted in an additional mean 10.1/5.3 mmHg BP reduction; this reduction was even greater (15.1/5.7 mmHg) among a separate group of severely hypertensive patients (i.e. SBP >170 mmHg or DBP >109 mmHg at baseline). Target BP was achieved in 54% of the ITT population. Both perindopril 4 mg/day and perindopril 8 mg/day were well tolerated and compliance was high throughout the study.

Conclusion: In the clinical outpatient setting, perindopril was found to be an effective dose-dependent and well tolerated antihypertensive treatment, with good compliance. Uptitration to the full therapeutic dosage of perindopril is an efficient approach for the management of a broad range of hypertensive patients without CAD.

Introduction

Hypertension is a global healthcare issue, and the worldwide prevalence is expected to increase by 60% during the next 15 years.[1] Although BP control is a crucial aspect of management, many hypertensive patients in primary healthcare remain poorly controlled following diagnosis. Among patients receiving treatment for their hypertension, levels of control

have been reported to be only 17% in Canada, and 5–29% in Europe, America, Asia, and Africa.[2] In the US, BP values of 140/90 mmHg or higher have been reported in over 90% of healthcare visits for treated hypertensive patients.[3] Reasons underlying the poor control of hypertension in primary healthcare include starting treatment too late, poor compliance with treatment, and confounding lifestyle factors. As acknowledged by guidelines,[4,5] full therapeutic dosages of antihypertensive agents, as well as combination therapy, represent valuable options to achieve BP targets.

Blockade of the renin-angiotensin-aldosterone system (RAAS) is a foundation therapy in the management of hypertension. Overactivity of the RAAS is involved in the pathogenesis of hypertension and its complications, as well as a range of other cardiovascular diseases. The most recent clinical guidelines recommend ACE inhibitors as first-line therapy for the management of hypertension in patients with a wide range of associated risk factors.[4]

In this report, we describe the findings of the CONFIDENCE (The Efficacy and Tolerability of Coversyl® now for Patients with Hypertension: Evidence-Based Medicine) study. This was an open-label, observational, phase IV trial examining the dose-dependent antihypertensive efficacy and tolerability of perindopril 4 and 8 mg/day, as well as compliance with treatment, in primary healthcare over 12 weeks. We selected the ACE inhibitor perindopril, since it is known to have an effective and long-lasting antihypertensive effect (trough : peak ratio of 70–100%),[6-10] and a good tolerability profile,[6-9] and has been proven to reduce the long-term risk of cardiovascular morbidity and mortality in a large range of hypertensive patients.[11-13]

Methods

Study Design

The CONFIDENCE study was a 12-week, prospective, open-label, multicenter, observational study involving 880 primary healthcare clinics and 113 specialists throughout Canada. An open-label design was chosen because phase IV clinical studies, particularly those involving general practitioners, allow the collection of data on the efficacy and safety of a given antihypertensive drug in heterogeneous cohorts of patients facing the current problems of daily clinical practice. In addition to several morbidity-mortality trials,[11-13] this observational survey with perindopril allows the definition of, among other issues, the weak points of the antihypertensive treatment approach, providing, for example, information on the awareness of the hypertensive state, BP control, and adherence to treatment.

The CONFIDENCE study conformed to the Declaration of Helsinki ethical principles for medical research involving human subjects and was approved by the Canadian Shield Ethics Review Board. Prior to enrollment in the study, patients were required to provide written informed consent.

Patients

The study cohort included men and women aged ≥18 years without CAD and with hypertension (i.e. SBP ≥140 mmHg and/or DBP ≥90 mmHg, or SBP ≥130 mmHg and/or DBP ≥80 mmHg for patients with diabetes mellitus),[5] whether untreated or inadequately managed with any previous antihypertensive treatment. Exclusion criteria included being currently prescribed perindopril, known intolerance to ACE inhibitors, use of potassium-sparing diuretics, serum elevations of liver enzymes and/or bilirubin, and impaired renal function (serum creatinine >177 μmol/L, serum potassium >5.5 mmol/L). Exclusion criteria also included severely hypertensive patients (SBP >170 mmHg or DBP >109 mmHg), a history of angioedema, diagnosis of CAD, history of myocardial infarction <3 months prior to the study, hypotension with SBP <110 mmHg, neutropenia/agranulocytosis, and pregnancy or breastfeeding.

Interventions

The CONFIDENCE trial was an outpatient-based, phase IV study conducted by the participating investigator. After baseline evaluations, patients included into the study were prescribed perindopril 4 mg (Servier, France) to be taken once daily each morning. Considering the fact that the study design was prospective and observational, previously treated patients did not undergo a wash-out phase, as this would have failed to replicate real-world clinical practice. Follow-up lasted 12 weeks, with visits at baseline (visit 1), between days 14 and 28 (visit 2), and at day 84 ± 14 days (visit 3) [figure 1]. Baseline BP was

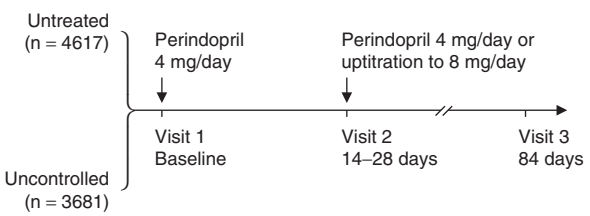

Fig. 1. Study design. **ACE** = angiotensin-converting enzyme; **ARB** = angiotensin II type 1 receptor antagonist (angiotensin receptor blocker); **BB** = β-adrenoceptor antagonist (β-blocker); **CCB** = calcium channel blocker.

measured at visit 1 while the patients were still on treatment with their previous therapy.

Among the patients already being treated at baseline, perindopril either directly replaced all previous ACE inhibitors or angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]), or was added to antihypertensive treatment with calcium channel blockers (CCBs), diuretics, or β-adrenoceptor antagonists (β-blockers).

For patients failing to achieve target BP at visit 2, perindopril was uptitrated to 8 mg/day for the remainder of the study according to the physician's judgment; patients with adequate BP control remained at 4 mg/day (figure 1). Throughout the follow-up period, no other changes in the treatment of hypertension were allowed, while treatment of other diseases was allowed at the discretion of the physician. At the end of the study at visit 3, patients with controlled BP continued their treatment with perindopril 4–8 mg/day, while patients with uncontrolled hypertension were treated according to their physician's judgment.

Efficacy Assessments

Efficacy endpoints in the overall population included reductions in SBP, DBP, and pulse pressure (defined as SBP – DBP) from baseline to visit 2 or visit 3, as well as the proportions of patients achieving target BP at visits 2 and 3. At each study visit, BP was measured in the morning, before administration of perindopril, after 5 minutes in the seated position using the auscultatory method with a properly calibrated and validated instrument. Two BP readings were taken and averaged. During the study, target BP was defined according to the 2006 Canadian Hypertensive Education Program (CHEP) guidelines,[5] i.e. <140/90 mmHg in the absence of target organ damage and associated clinical conditions, or <130/80 mmHg in the presence of diabetes, renal disease, or proteinurea.

In the adverse event assessment performed at each follow-up visit, any adverse events were recorded by the treating physician on the patient's safety case report form. At visits 2 and 3, tolerance to both dosages of perindopril was rated as excellent, very good, good, moderate, or poor by the treating physician. Compliance with study treatment was also evaluated at visits 2 and 3 by counting missed doses.

Statistical Analyses

Efficacy analyses were performed on the intent-to-treat (ITT) population. The changes in quantitative variables were evaluated by Student's t-test comparison of means. Data are

Table I. Baseline characteristics in the intent-to-treat population[a]

Characteristic	Patients prescribed perindopril (n = 8298)
Demographics	
Males	4196 (51)
Age, y (mean ± SD)	59.1 ± 13.1
<55	3151 (38)
55–65	2348 (29)
65–75	1694 (21)
>75	1023 (12)
Ethnicity	
Caucasian	6236 (75)
Asian	1320 (16)
Black	227 (3)
other	515 (6)
Disease characteristics	
SBP, mmHg (mean ± SD)	152.5 ± 10.8
DBP, mmHg (mean ± SD)	89.5 ± 9.0
Inactive[b]	281 (34)
Type 2 diabetes mellitus	2064 (25)
Age >55 y male/>65 y female	4066 (48)
Smokers	1329 (16)
Family history of CVD	1270 (15)
Dyslipidemia[c]	1060 (13)
Abdominal obesity[d]	2440 (29)
Risk factors additional to hypertension	
No risk factors	2324 (28)
1 risk factor	2306 (28)
2 risk factors	1915 (23)
3 risk factors	1127 (14)
4 risk factors	436 (5)
5 risk factors	190 (2)
Treatment status	
Untreated hypertension	4617 (56)
Uncontrolled hypertension	3681 (44)
switch from ACE inhibitor/ARB	1767 (21)
previous ACE inhibitor	1340 (16)
previous ARB	434 (5)
discontinued CCB, BB, or diuretic	403 (5)
concomitant diuretic	1414 (17)
concomitant BB	712 (9)
concomitant CCB	966 (12)
monotherapy	2217 (26)

Continued next page

Table I. Contd

Characteristic	Patients prescribed perindopril (n = 8298)
2 antihypertensive drugs	966 (12)
3 antihypertensive drugs	415 (5)
≥4 antihypertensive drugs	83 (1)

a Values are n (%) unless stated otherwise.

b Patients were asked the question "are you physically active?" at baseline.

c Total cholesterol/high-density lipoprotein cholesterol ratio ≥6.

d Waist circumference >102 cm for men and >88 cm for women.

ARB = angiotensin II type 1 receptor antagonist (angiotensin receptor blocker); **BB** = β-adrenoceptor antagonist (β-blocker); **CCB** = calcium channel blocker; **CVD** = cardiovascular disease.

expressed as mean ± SD or as the number and proportion of patients [n (%)]. Significance was defined as a p-value of <0.05.

Results

Population Characteristics

A total of 8298 patients were recruited by 880 general practitioners and 113 specialists across Canada. The baseline characteristics and the previous antihypertensive strategies for the patient population are shown in table I. The patients had a mean age of 59 years and 51% were male. The majority of the patients recruited were of Caucasian ethnicity (75%), and the next most common ethnicity was Asian (16%). Fifty-six percent of patients were previously untreated for their hypertension. The mean SBP/DBP at baseline in the whole population was 152.5/89.5 mmHg. A complementary analysis was performed in an additional population of severely hypertensive patients (identified with SBP >170 mmHg or DBP >109 mmHg) who differed from the main population by having a mean SBP/DBP at baseline of 178.1/97.6 mmHg. This population was of clinical relevance given the number of patients (n = 666) and their elevated cardiovascular risk due to their high BP levels.

Overall, 79% of patients had up to two cardiovascular risk factors (table I). At study entry, 25% of patients were diagnosed with type 2 diabetes. After starting study treatment with perindopril 4 mg/day, 63% of patients overall were on monotherapy and 37% on at least two antihypertensive drugs. The dosage had been increased to 8 mg/day among 23% of patients at visit 2. At visits 2 and 3, respectively, 706 and 1759 patients had discontinued the study. The main reasons reported for discontinuation were loss to follow-up (n = 282), patient's withdrawal of consent (n = 66), non-compliance with study treatment (n = 83), violation of study protocol (n = 833), adverse events or serious adverse events (n = 457), and lack of drug efficacy (n = 38).

Efficacy Outcomes

BP Reduction in the Overall Population

A total of 6536 patients had their BP evaluated at all three time points and constituted the efficacy population. In the overall population, mean SBP and DBP were lowered throughout the study (figure 2). At visit 2, between 14 and 28 days after

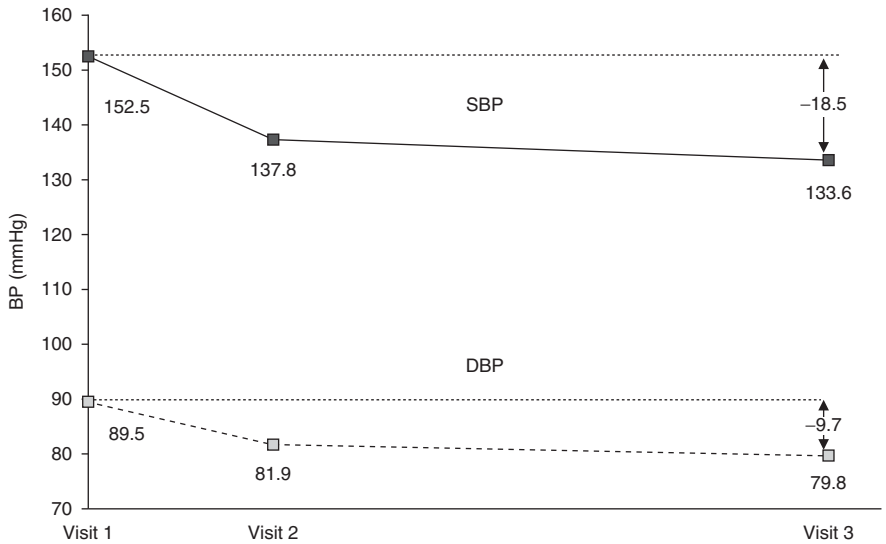

Fig. 2. Change in mean SBP and DBP for the overall population from the start of study treatment with perindopril (visit 1, baseline) until the end of the study (visit 3, day 84). * $p < 0.001$ vs baseline.

Table II. Mean SBP, DBP, and pulse pressure at baseline, visit 2, and visit 3 in the overall hypertensive population and in the Asian and diabetic subpopulations, as well as in the separate severely hypertensive population[a]

Population	Visit 1 (baseline)			Visit 2 (14–28 days)			Visit 3 (84 days)					
	SBP (mmHg)	DBP (mmHg)	pulse pressure (mmHg)	SBP (mmHg)	DBP (mmHg)	pulse pressure (mmHg)	SBP (mmHg)	SBP reduction from baseline (mmHg)	DBP (mmHg)	DBP reduction from baseline (mmHg)	pulse pressure (mmHg)	control rate (%)
Overall hypertensive population (n = 8298)	152.5 ± 10.8	89.5 ± 9.0	63.0	137.8 ± 13.9	81.9 ± 9.2	55.9	133.6 ± 12.6	18.5*	79.8 ± 8.4	9.7*	54.2	54
Diabetic subpopulation (n = 2064)	148.9 ± 11.2	86.1 ± 8.9	62.8	135.5 ± 13.0	79.6 ± 8.8	55.9	132.4 ± 12.1	16.5*	78.1 ± 8.1	8*	54.3	23.4
Asian subpopulation (n = 1320)	150.0 ± 11.1	89.4 ± 8.6	60.6	135.8 ± 13.5	81.9 ± 8.7	53.9	131.8 ± 12.9	18.2*	79.7 ± 8.0	9.7*	52.1	43.8
Severely hypertensive population (n = 666)	178.1 ± 11.2	97.6 ± 12.1	80.5	149.7 ± 17.4	85.8 ± 10.7	63.9	141.9 ± 15.8	36.2*	82.3 ± 10.0	15.3*	59.6	35.1

a Values for BP are mean ± SD.

* $p < 0.0001$ vs baseline.

starting perindopril, the mean SBP/DBP had reduced to 137.8/81.9 mmHg (table II). After 12 weeks of perindopril-based therapy (visit 3), mean BP had decreased to 133.6/79.8 mmHg – i.e. a reduction of 18.5/9.7 mmHg ($p < 0.001$). At every follow-up visit, the sustained decrease in SBP and DBP versus baseline was significant (all $p < 0.0001$). Pulse pressure also decreased throughout the study (table II). Among the 23% (n = 1943) of patients who had their dosage uptitrated to 8 mg/day at visit 2, SBP/DBP decreased from 146.7 ± 11/86.3 ± 8.8 mmHg to 136.6 ± 11.8/80.9 ± 8.3 mmHg at visit 3 (figure 3).

The proportion of patients achieving the target BP of <140/90 mmHg (or <130/80 mmHg with associated clinical conditions) in the overall population was 40% at visit 2, and this had further increased to 54% by visit 3. A total of 1943 patients were uptitrated to perindopril 8 mg/day. Of these, a further 42% had normalized BP at the end of the study.

BP Reduction in the Diabetic, Asian, and Severely Hypertensive Populations

In the diabetic subpopulation, a category of patients in whom it is known to be difficult to normalize BP, the mean baseline BP significantly decreased by 16.5/8 mmHg, while in the Asian subpopulation, mean baseline BP decreased by 18.2/9.7 mmHg (table II). In the severely hypertensive group, the mean BP reduction was 36.2/15.3 mmHg from baseline (table II). Uptitration of perindopril to 8 mg/day at visit 2, in this group, resulted in an additional 15.1/5.7 mmHg decrease in BP by the end of the study (from 182.4/99.1 mmHg to 159.3/90.1 mmHg at visit 2 to 144.8/83.8 mmHg at visit 3) [figure 3]. As with the overall population, pulse pressure in all of these patient groups decreased throughout the study (table II).

BP Reduction Among Patients According to Previous Management

Reductions in mean BP and BP normalization according to previous management are shown in table III. For untreated patients, the initiation of perindopril decreased BP by a mean of 21.5/11.1 mmHg. For patients previously treated with other ACE inhibitors, switching to perindopril 4–8 mg/day reduced baseline BP by a mean of 15.5/7.7 mmHg at visit 3 (table III). Within this subgroup, 56% of the patients were receiving ramipril at a mean dose of 8.4 mg/day and benefited from an additional 13/6 mmHg mean decrease in BP after switching to perindopril. Replacing ARBs with perindopril further reduced baseline BP by a mean of 15.9/8.2 mmHg (table III), and this additional BP decrease was observed whatever the previous ARB (table IV). The most commonly used ARBs were valsartan (20% of patients) and telmisartan (17% of patients), which were being prescribed at mean daily doses of 121 mg and 78 mg, respectively.

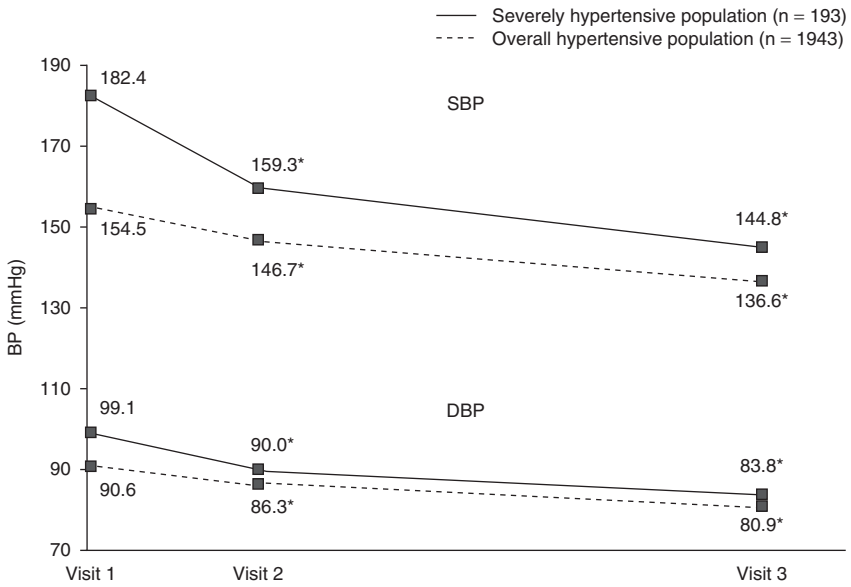

Fig. 3. Change in mean SBP and DBP for the overall population and for the separate population of severely hypertensive patients who were uptitrated from perindopril 4 to 8 mg/day at visit 2. * $p < 0.001$ vs baseline.

Tolerability and Treatment Adherence

In total, 12.4% of patients discontinued therapy with perindopril, principally because of adverse events (5.5% of patients), patient loss to follow-up (3.4%), non-compliance (1%), and patient withdrawal of consent (0.8%). Throughout the study, both doses of perindopril were very well tolerated, with over 90% of the ITT population reporting at visit 3 good to excellent tolerance (figure 4). During study treatment, the most frequently reported adverse events leading to treatment

Table III. Mean reductions in BP with perindopril for treatment-naïve patients or subgroups of patients who were previously unresponsive to other antihypertensive treatments[a]

Population	Visit 1 (baseline)		Visit 2 (14–28 days)		Visit 3 (84 days)				
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	reduction from baseline (mmHg)	DBP (mmHg)	reduction from baseline (mmHg)	control rate (%)
Naïve subpopulation (n = 4617)	155.2 ± 13.1	91.8 ± 9.2	137.7 ± 14.2	82.9 ± 9.2	133.8 ± 12.9	21.5 ± 14.8*	80.6 ± 8.4	11.1 ± 9.5*	SBP 61 DBP 74
Switched from ACE inhibitors (n = 1340)	149.3 ± 11.1	86.3 ± 8.8	137.7 ± 13.9	80.5 ± 8.8	133.5 ± 12.3	15.5 ± 13.8*	78.5 ± 8.5	7.7 ± 9.4*	48
Switched from ARBs (n = 434)	151.9 ± 11.2	87.5 ± 9.0	137.4 ± 12.1	80.8 ± 8.5	135.5 ± 12.3	15.9 ± 14.3*	79.3 ± 8.2	8.2 ± 9.1*	46
Added to BB[b] (n = 639)	153.3 ± 10.9	87.0 ± 9.9	139.3 ± 10.9	80.0 ± 9.8	135.5 ± 13.4	17.7 ± 14.8*	78.4 ± 8.7	8.7 ± 9.8*	46
Added to CCB[b] (n = 881)	152.6 ± 10.5	86.2 ± 9.8	139.0 ± 13.2	79.7 ± 9.7	135.5 ± 12.8	17.0 ± 14.7*	78.1 ± 9.2	8.2 ± 10.0*	47
Added to diuretics[b] (n = 1256)	152.2 ± 10.5	87.5 ± 9.6	138.6 ± 13.8	80.8 ± 9.2	134.7 ± 12.2	17.6 ± 13.7*	79.0 ± 8.4	8.5 ± 9.6*	51

a Values for BP are mean ± SD.

b Patients treated with β-adrenoceptor antagonist (β-blocker; BB), calcium channel blocker (CCB), or diuretic could also be receiving concomitant treatment with another class of antihypertensive.

ARB = angiotensin II type 1 receptor antagonist (angiotensin receptor blocker); * $p < 0.001$ vs baseline.

Table IV. Mean reductions in BP and proportion of patients achieving target BP for patients who were switched to perindopril having been previously unresponsive to treatment with different angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs])[a]

ARB (dose range)	Visit 1 (baseline)		Visit 2 (14–28 days)			Visit 3 (84 days)		
	SBP (mmHg)	DBP (mmHg)	SBP reduction from baseline (mmHg)	DBP reduction from baseline (mmHg)	patients achieving target at visit 2 (%)	SBP reduction from baseline (mmHg)	DBP reduction from baseline (mmHg)	patients achieving target at visit 3 (%)
Valsartan (60–160 mg/day)	150.2 ± 11.6	87.8 ± 9.4	12.7 ± 12.1*	8.2 ± 9.2*	37	15.1 ± 14.3*	9.7 ± 8.3*	47.8
Telmisartan (40–80 mg/day)	151.1 ± 11.4	85.4 ± 9.9	10.9 ± 12.1*	5.5 ± 8.3*	34	13.1 ± 13.8*	6.2 ± 9.2*	40.0
Irbesartan (150–300 mg/day)	150.7 ± 12.5	85.0 ± 10.3	12.5 ± 13.1*	6.7 ± 7.9*	37	15.6 ± 14*	8.1 ± 9.4*	49.1
Losartan (50–100 mg/day)	149.8 ± 12.7	84.3 ± 9.1	12.9 ± 11.8*	5.5 ± 6.8*	36	15.2 ± 14*	6.1 ± 9.7*	43.8

a Values for BP are mean ± SD.

* $p < 0.001$ vs baseline.

discontinuation were cough (4.1% of patients), headache (0.4% of patients), and dizziness (0.3% of patients) [table V].

Compliance with treatment was high throughout the study. At visit 3, 71% of patients had not missed any doses of perindopril, while 22% of patients had missed between one and five doses. Compliance at the end of the study was also significantly higher among patients who had achieved target BP at visit 2 (74% had no missed doses) compared with patients failing to achieve target BP (69% had no missed doses, $p < 0.0001$).

Discussion

The CONFIDENCE trial confirms the dose-dependent antihypertensive efficacy and tolerability of perindopril 4–8 mg/day in primary healthcare. Over half of the patients achieved target BP in a relatively short time (12 weeks), which is above the observed average BP control rate.[2] Clinically relevant reductions in BP and resultant BP control were obtained in both newly diagnosed and previously treated patients. The relatively lower BP control rate among diabetic patients reflects the more stringent BP target and the need for combination therapy in these patients. Despite being part of the protocol, the use of uptitration (23%) and the use of more than one antihypertensive drug (37%) were low during the trial. More extensive use of uptitration would have certainly improved the control rate observed in the study. The tolerability profile of both perindopril dosages was good, and the low rate of cough due to perindopril is in line with a recent meta-analysis that reports that perindopril has a very low incidence of cough compared with the other commonly used ACE inhibitors.[14]

Some previous trials with perindopril and a meta-analysis of individual data showed a similar dose-dependent efficacy in a broader range of patients with or without previous CAD.[8,15,16] In this regard, the CONFIDENCE trial is the first demonstration of the dose-dependent effect of perindopril among hypertensive patients free of CAD.

In the CONFIDENCE study, uptitration to perindopril 8 mg/day provided an additional mean 10.1/5.3 mmHg BP

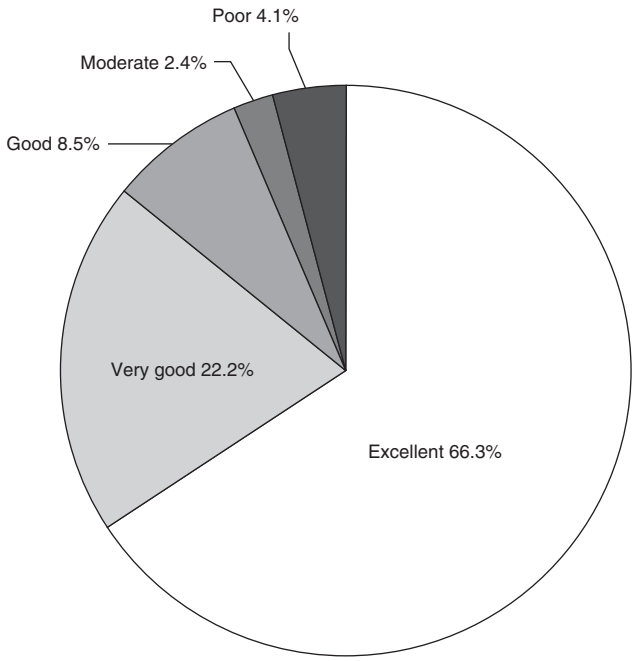

Fig. 4. Tolerability of perindopril 4–8 mg/day in the overall population at visit 3.

Table V. Most frequently reported adverse events leading to treatment discontinuation

Adverse event	Frequency (%)
Cough	4.1
Headache	0.4
Dizziness	0.3
Fatigue	0.2
Nausea	0.2
Itchy/dry/irritated throat	0.2
Diarrhea	0.1
Gastrointestinal upset	0.1
Light-headedness	0.1
Not specified	0.1

reduction compared with perindopril 4 mg/day, which is even greater (15.1/5.7 mmHg) among severely hypertensive patients (i.e. SBP >170 mmHg or DBP >109 mmHg at baseline). High doses of perindopril are known to provide more complete ACE inhibition than lower doses[17] and uptitration of perindopril from 4 to 8 mg/day has been shown to double the antihypertensive efficacy in response to exogenous angiotensin I.[18] In another observational study, uptitration to perindopril 8 mg/day as part of a multifactorial intervention in patients with mild-to-moderate hypertension and additional cardiovascular risk factors (including ischemic heart disease in 72% of patients) was reported to produce a mean 33/16 mmHg decrease.[15] In that study, 86% of patients achieved target BP levels. Uptitration to perindopril 8 mg/day has also been associated with a further reduction in arterial stiffness in diabetic hypertensive patients,[19] which may have important long-term implications, as reduced arterial compliance is a strong predictor of cardiovascular events.

In the CONFIDENCE trial, the further antihypertensive efficacy of perindopril in patients previously treated with ACE inhibitors and ARBs may be explained by an increase in adherence throughout the study, and also by the long duration of action with perindopril (trough : peak ratio of 70–100% for perindopril, versus ramipril 50–60%, and versus the majority of the ARBs),[10] and its high affinity for both circulating and tissue ACE.[20]

In addition, the CONFIDENCE results are comparable to those from other large-scale primary healthcare trials with perindopril.[6-8,21] In one study, perindopril was administered to over 13 000 hypertensive patients for 12 weeks.[6,7] Patients who were previously unresponsive to ARBs were found to obtain a further mean 16.2/9.4 mmHg BP decrease when they were switched to perindopril,[6] in line with our results. In a recent trial, perindopril arginine (5–10 mg/day), a new formulation that improves the stability of perindopril and is available in most countries,[22] replaced other ACE inhibitors in patients with uncontrolled hypertension (n = 824).[21] After 3 months, over half of the patient population had achieved target BP (<140/90 mmHg), with a mean BP decrease of 26/16 mmHg.

Aside from its antihypertensive effect, perindopril, in combination with amlodipine (in ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial]) or indapamide (in ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation] and HYVET [Hypertension in the Very Elderly Trial]), has been consistently associated with significant reductions in mortality as well as improvements in cardiovascular outcomes in hypertensive patients.[11-13,23] Notably, the ASCOT and the HYVET were both stopped prematurely due to a clear reduction in total mortality in favor of the perindopril-based regimen.

The open-label design and the lack of a control group of patients are potential limitations to our study, as they are for all observational studies. Another limitation is the high rate of patient dropout at visits 2 and 3, which is typical for a phase IV study of this kind and may reflect real clinical practice.[24] On the other hand, compliance with treatment in the patients remaining in the study and BP reduction and control may have been improved as a result of care and attention from the treating physician. Despite these limitations, observational studies of primary healthcare populations remain a useful source of information, as they examine a spectrum of patients representative of the hypertensive population treated in daily clinical practice. In this way, they complement the multicenter, randomized, morbidity-mortality trials that assess the impact on major cardiovascular events.

Conclusion

This large community-based study indicates that perindopril 4–8 mg/day is a dose-dependent, effective, and well tolerated antihypertensive treatment in real daily practice. This study is the first demonstration of the antihypertensive benefits of uptitration to perindopril 8 mg/day in hypertensive patients without CAD. Therefore, uptitration to the full dose of perindopril may be considered as an effective approach for improving the management of hypertensive patients.

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